CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
NORFLURAZON

Chemical Code # 2019, Tolerance # 356
SB 950 # 287

March 18, 1987
6/10/88, 10/28/92 and 3/12/01

I. DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effect
Chronic dog:	No data gap, no adverse effect
Oncogenicity rat:	No data gap, no adverse effect
Oncogenicity mouse:	No data gap, possible adverse effect
Reproduction rat:	No data gap, no adverse effect
Teratology rat:	No data gap, no adverse effect
Teratology rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.
All record numbers through 163194 in 356-120 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T010312
Original Toxicology Summary indexed by R. Marovich, and summary completed by J. Gee. Revisions by C. Aldous, 6/10/88; H. Green and J. Gee, 10/28/92; J. Gee, 3/12/01

***** NOTE: This Summary was edited to add EPA "Core" classifications on 01/10/90.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED RAT

**** 002-006 961757** "Two Year Feeding Study in Rats". (WARF Institute, 4/29/75) Norflurazon technical, 98.8%, was fed at 0, 125, 375 or 1025 ppm in the diet. Animals were from F1a offspring of F0 animals who had been dosed for 18 weeks prior to mating in the reproduction study (record # 961762). Possible adverse effect: accelerated aging reported especially in high dose males. NOEL = 375 ppm (increased organ weights). No evidence for oncogenicity. Acceptable study. J. Remsen (Gee), 7/16/85.

EPA one liner: NOEL = 375 ppm. (Increased liver, kidney and ovary weights, fatty changes in adrenals, endometritis, increased chromophobe adenomas in pituitary, modular or cordical [sic] hypertrophy in adrenals, casts in kidneys. No core grade.)

NOTE: EPA Norflurazon "Guidance" document of 1984 indicated that all chronic and oncogenicity data requirements were filled. This was one of the submitted studies.

002-005 961755-961756, 961760, 961770, 961772, 961781-83. Individual data for 006 961757, above.

017 961764 A subchronic study, spin-off from the reproduction study, 013:961762. Study used F0 rats maintained for 9 months on diets with high dose = 500 ppm. No CDFA review performed or needed: an acceptable combined rat study exists, which employed a more rigorous dosage range.

CHRONIC DOG

018, 051 031087 "San 9789 (Zorial*), 6-Month Feeding Study in Dogs." (Presumed performed by Sandoz Ltd. Basle, Switzerland, Report No. 9789-825, 10/9/73). San 9789, purity not given, was fed in the diet to beagles, 4/sex/group, at 0, 50, 150 or 450 ppm. Apparent NOEL = 150 ppm, based on increased liver weight and increased number of colloid vacuoles in the thyroid. Normal weight gain, behavior, hematology and urinalysis were reported. **Unacceptable, not upgradeable in lieu of a chronic study.** Six-month studies of this time period were not evaluated by CDFA [DPR] as substitutes for chronic studies, the dose range was too low to effectively evaluate chronic toxicity, there was no analysis of diet, there were no daily observations, and no eye exam results. Other deficiencies were indicated in the worksheets. Possible treatment-related effects were noted at high dose level, however **no adverse effects were indicated**. C. Aldous/D. Shimer, 6/10/88. This study was discussed on 1/10/90 by CDFA in response to an EPA memorandum of 1/30/89.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/30/89) notes EPA classification as "Core Minimum".

EPA 1-liner: NOEL = 150 ppm. LEL = 450 ppm (congestion of the liver, hepatocyte swelling and

increased liver weights increase in colloid vacuole in thyroid.)

356-120 163194 This was the same study as reported in 031087 above. (Gee, 3/9/01)

** 356-065 088787 "A One Year Feeding Study in Beagle Dogs to Evaluate Chronic Toxicity". (Simon F. P. Warren et al., Sandoz Agro Ltd., Basel, Switzerland, Project # 422-D, July, 1990). Norflurazon, 98.2% purity, was fed in the diet for 52 weeks at 0 (basal diet), 50, 200, or 800 ppm to 4 Beagle dogs/sex/group. NOEL = 50 ppm (increased degree of renal cortical tubular pigmentation at 200 and 800 ppm in males). There were several notable findings at 800 ppm. Body weight gain differences were not statistically significant, but decrements of about 2 kg in high dose males suggested a treatment effect. There were modest reductions in food consumption in both sexes at 800 ppm. Major hematology parameters (RBC count, HCT, and Hb concentration) were often slightly reduced at 800 ppm in both sexes. One male and one female at 800 ppm had noteworthy hepatitis attributed to treatment; conditions were more severe in the female, which had fibrosis, altered lobular structure, focal necrosis, biliary hyperplasia, and marked pigmentation of Kupffer cells by hemosiderin. Gall bladder mucinous hyperplasia was increased in frequency and/or severity in 800 ppm males and females. **No adverse effects** were indicated. **Acceptable**. (H. Green and J. Gee, 10/27/92)

ONCOGENICITY, MOUSE

**** 010 961761** "Two Year Feeding Study in Mice. [Final Report]" (WARF Institute, 8/5/75) Norflurazon technical, 98.8%, was fed at 0, 85, 340 or 1360 ppm in the diet to 125/sex/dose group and a total of 250/sex as controls. Animals were from the F1 offspring of F0 animals which were dosed for 18 weeks prior to mating. Possible adverse effect: liver hypertrophy and hepatomas in high dose males. NOE = 340 ppm (hepatoma/hypertrophy). Acceptable study. J. Remsen (Gee) 7/16/85.

EPA one liner: NOEL: 340 ppm (Hepatoma/hyperplasia-hypertrophy)

NOTE: EPA Norflurazon "Guidance" document of 1984 indicated that all chronic and oncogenicity data requirements were filled. This was one of the submitted studies. That document stated, regarding increased liver tumors: "this is not a potential carcinogenic response, but a toxic response to rather high level of chemical insult" (p. 6 of "Guidance" document, Dec. 1984).

007-009, 011-012, 019 961758-59, 961767-69, 961761, 961771, 961774, and 961777-79. Individual data for 010: 961761, above.

010 961773 Overview on hepatomas in males, related to 010:961761, above.

356-119 163193 “Assessment of the data derived from a histologic examination of liver tissues and certain lung tissues taken from male mice participating in a two-year oral carcinogenicity study (Sandoz Project T-204) with a substance identified by 9789” (Rust, J. H., Sandoz, Inc., Project T-1-8/26/80, 8/26/80) The submission contained two reports, one consisting of a re-examination of the livers of male mice and the second, a statistical analysis of the findings. The conclusion was basically the same as with the original study review. There was a statistically significant increase in hepatocellular adenomas (hepatomas) in high dose males but no dose-related increase in hepatocellular carcinomas. The study remained acceptable with a possible adverse effect. (Gee, 3/12/01).

REPRODUCTION STUDIES

RAT

** 072 112019 "Norflurazon - Two Generation Reproduction Study in Rats" (B. Eschbach, et al, Sandoz Agro Ltd., Basle, Switzerland, report # 91/125, December 1991) Norflurazon (SAN 9789 H), 98.1% purity (analysis # 24812), was fed in the diet through 2 generations with two litters per generation at 0 (powdered standard Kliba 343 rat maintenance diet), 150, 750, and 1500 ppm with 25 Wistar Crl:(WI)br (outbred, SPF Quality) rats per sex per group and an additional untreated health screen group of 5 per sex. Treatment began 70-days and 84-days pre-mating for F0 and F1 parents respectively. Increased absolute and relative liver and kidney weights were noted in parental F0 and F1 animals of both sexes at 750 and 1500 ppm and in pups. Reduced 21-day F2b pup weights at 750 and 1500 ppm and reduced F2b survival at 1500 ppm may have been treatment-related. **Chronic**: necrosis and hepatocellular hypertrophy in the liver of F0 and F1 parental rats of both sexes at 750 and 1500 ppm and chronic progressive nephrosis in F0 and F1 parental males principally at 1500 ppm were reported. Parental NOEL = 150 ppm. Reproductive NOEL = 150 ppm (Reduced 21-day F2b pup weights at 750 and 1500 ppm, effects on liver and kidney weights). **Acceptable.** (H. Green and Gee, 7/20/92)

013 961762 "Compound 9789: Reproduction Studies in Rats and Mice" (WARF Institute, 4/29/75) Norflurazon technical, 0, 125, 250 or 500 ppm was fed in the diets of F0 (Sprague-Dawley) rats, then increased to 0, 125, 375 or 1025 ppm for F1 rats at weaning. The latter dosages were maintained throughout the balance of the study. Previously classified as unacceptable with possible adverse effect [J. Remsen (Gee), 7/16/85]. Subsequent new submissions were received (Volumes 42, 43, 50). Data were re-evaluated in the 3/18/87 CDFA rebuttal response by J. Gee, and in a 6/3/88 review by C. Aldous. The latter review confirmed **unacceptable, non-upgradeable** status, and **removed** "possible adverse effects" flag, due to the limited nature of evidence of a treatment effect. Major deficiencies of study were: (1) dosage range was not justified with respect to an MTD, and (2) there was no microscopic examination of adults which had been dosed above 500 ppm. Apparent NOEL = 375 ppm (based on **limited** evidence of slightly reduced fertility, gestation and viability indices at 1025 ppm).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/30/89) notes EPA classification as "Core Minimum".

EPA one liner: NOEL: 375 ppm (reduced fertility, gestation and viability indices).

042 050588 (ADDENDUM TO 961762) Contained rebuttal remarks to the CDFA [DPR] review and duplicate copies of 961762 and 961757. No change in status. (See CDFA rebuttal response document of 3/18/87).

043 050591 (supplement to 961762) "9 Month Feeding Study in Rats: F0 Generation" (WARF Institute, 8/25/72) Norflurazon technical, 98.8%, was fed at 0, 125, 250, 500 ppm in the diet. F0 animals were from the rat reproduction study #961762. Not acceptable to fill chronic or reproduction study data requirements. **No adverse effects indicated**. Reproductive NOEL $\geq$ 500 ppm (HDT). J. Gee, 3/11/87.

EPA one liner: NOEL = 500 ppm. NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/30/89) notes EPA classification as "Core Supplementary".

050 057232 Repeat submissions of rebuttal remarks, same as 042:050588, but with editing of minor errors (considered in June, 1988 re-review, above).

MOUSE

014 961763 "Reproduction Studies in Rats and Mice Final Report Volume II." (WARF Institute, 4/29/75) Norflurazon technical, 98.8%, was fed at 0, 85, 170 or 370 ppm in the diet for one generation only in two year chronic study. High dose was too low. Insufficient data for assessment with no adverse effect indicated. Reproductive NOEL $\geq$ 370 ppm (HDT). **Unacceptable and not upgradeable**. J. Remsen (Gee) 7/16/85.

EPA one liner: NOEL > 370 ppm (HDT). NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/30/89) notes EPA classification as "Core Supplementary".

TERATOLOGY, RAT

** 016 961754 "Compound 9789: Investigation of Teratogenic Potential in the Rat". (Sandoz Biological Research Department, 8/7/82). Norflurazon technical (purity not stated) was given at doses of 0, 100, 200 or 400 mg/kg/day by oral gavage. Decreased weight gain in dams at all test doses. **No compound-related developmental effects** were noted. Developmental NOEL $\geq$ 400 mg/kg/day (HDT). **Acceptable study**. J. Remsen (Gee) 7/16/85.

EPA one liner: Teratogenic NOEL > 400 mg/kg/day (HDT)

013 033585 "Reproduction Studies in Rats and Mice Final Report Volume I." (WARF Institute, 4/29/75) Norflurazon technical, 98.8%, was fed at 0, 125, 375 or 1025 ppm in the diet. No maternal toxic effects were noted at the high dose. No developmental effects were noted. **Unacceptable, not upgradeable** (limited design: spin-off from a reproduction study. An acceptable study with much more rigorous dosage range is available in 016:961754). J. Remsen (Gee) 7/16/85.

EPA one liner: Teratogenic NOEL > 1025 (HDT)

TERATOLOGY, RABBIT

** 044 050592 "Investigation of Teratogenic Potential of Norflurazon in the Rabbit - Segment II". (Sandoz T-1794; Sandoz Pharmaceutical R&D, 8/31/83). Norflurazon technical lot # 80561, 98.4%, was given at doses of 0, 10, 30 or 60 mg/kg/day by oral gavage. The material was fetotoxic at the high dose with dose-related delayed development. No other developmental effect was reported. Fetotoxic NOEL= 10 mg/kg/day (delayed ossification). Maternal NOEL = 30 mg/kg (decreased weight gain). Teratogenic NOEL $\geq$ 60 mg/kg/day (HDT). **No adverse developmental effects indicated. Acceptable** study. J. Gee, 3/10/87.

EPA one liner: Teratogenic NOEL: > 60 mg/kg; Maternal NOEL = 30 mg/kg (decreased weight gain); Fetotoxic NOEL = 10 mg/kg (LTD; decreased weight, incomplete ossified variations) EPA Guideline study.

356-118 163192 "Dose range-finding study of norflurazon in pregnant rabbits." (Hrab, R., Sandoz, Inc., study no. T-1-4/19/83, completed 4/19/83) New Zealand White rabbits, 5 per dose, were given doses of norflurazon (technical, lot # 80561, 98.4% purity) at 0 (1% CMC plus 0.2% Tween 80), 10, 40, 80, 100 or 400 mg/kg/day by oral gavage on days 7 through 19. All 5 animals died or were sacrificed moribund at 400 mg/kg/day. Clinical signs at 80 and above included decreased locomotor activity, small amount of feces and statistically significant body weight loss. Increases in resorptions were noted at 80 and 100 mg/kg/day. No worksheet. **Supplemental study.** (Gee. 3/9/01).

GENE MUTATION

029 961784 "Mutagenicity Evaluation of Norflurazon Final Report." (LBI Project 2683, Litton Bionetics, 6/3/77) Norflurazon (no purity stated) was tested at 0, 0.1, 10, 100, 500 or 1000 ug/plate ±S9 with Salmonella strains TA1535, TA1537, TA1538, TA98, TA100, reported as single values only. No comment on toxicity but no mutagenic effects were reported. Unacceptable and not upgradeable. (J. Remsen (Gee) 7/16/85.)

EPA one liner: Negative mutagen.

038 036173 "Mutagenicity Evaluation by the Ames Test of Norflurazon." (Litton Bionetics, 5/77) Norflurazon (no purity stated) was tested with Salmonella strains of TA1535, TA1537, TA1538, TA98, TA100 ±rat liver S9 at 0, 1.0, 10, 100 or 500 µg/plate, single plate, single trial except for 3 concentrations (100, 500, 1000 µg/plate) with TA1537. No increase in reversion rate WAS reported. Inadequate high concentration without cytotoxicity or solubility justification. Unacceptable and not upgradeable. (J. Remsen (Gee) 12/27/85)

EPA one liner: Negative mutagen.

** 036 053028 "Salmonella/Mammalian Microsome Plate Incorporation Mutagenicity Assay." (Microbiological Associates (MBA#T5284.501014) 12/31/86) Norflurazon technical TR5-110586, was tested at 0, 667, 1000, 3333, 6667 or 10,000 µg/plate ± rat liver S9, 3 replicates, with *Salmonella* strains TA1535, TA1537, TA1538, TA98, TA100. A precipitate was seen at ≥ 1000 mg/plate. No increase in reversion rate in two trials was reported. Acceptable study. (J. Gee 3/10/87).

EPA one liner: none on file.

038 036171 "Report on Mutagenicity Test on NP-5 in Bacteria." (Biosafety Research Center, 10/20/80) Norflurazon technical, 99.8%, was tested at 0, 5, 10, 50, 100, 500, 1000 or 5000 µg/plate with *Salmonella* strains TA1535, TA1537, TA1538, TA98, TA100 +/- rat liver activation. No comment on toxicity or solubility. No increased reversion rate was reported. Unacceptable and not upgradeable. (J. Remsen (Gee) 12/27/85)

EPA One liner: Negative in tested strains.

045 050595 1-page reference from 1984 EPA Registration Standard Guidance document, noting that several negative bacterial gene mutation studies had been evaluated, and that one (apparently 029:961784) was found acceptable by EPA.

CHROMOSOMAL ABERRATION

** 045 050593 "Norflurazon Technical Chromosomal Aberrations in CHO Cells." (Microbiological Associates T4030-337, 10/10/85) Norflurazon technical, 97.9%, batch 1174-85, was tested at 0, 125, 250, 500 or 1000 µg/ml with S9 activation and at 0, 63, 125, 250 or 500 µg/ml without activation, with two flasks per concentration. A precipitate was noted at ≥ 250 µg/ml with cycle delay at 500 µg/ml without activation. No effect of exposure was reported. Acceptable study. (J. Gee, 3/10/87.)
EPA one liner: none on file.

DNA DAMAGE STUDIES

** 045 050594 "Norflurazon Technical Unscheduled DNA Synthesis in Rat Hepatocytes". (Microbiological Associates, 12/10/85) Norflurazon technical, 97.9%, was tested at 1.0, 3.3, 10.0, 33, 100, 333 or 1000 µg/ml with 3 and 10 µg/ml DMBA as the positive control,. Three replicates per concentration with no significant increase in unscheduled DNA synthesis at tests up to 333 µg/ml (1000 µg/ml were unreadable). Acceptable study. (J. Gee 3/10/87.)
EPA one liner: none on file.

038 036172 "Report on Mutagenicity Test on NP-2 in Bacteria". (Biosafety Research Center, 10/20/80) Norflurazon technical, 99.8% (NP-52), was tested with *B. subtilis* strains H17 and M45 by the disk assay at 0, 500, 1000, 5000 or 10,000 µg/disk without activation. There was no repeat trial. Kanamycin and mitomycin C were used as controls. There was no evidence of an adverse effect. Inadequate protocol, unacceptable and not upgradeable study. (J. Remsen (Gee) 12/27/85.)
EPA one liner: Negative in tested strains.

NEUROTOXICITY

Not required at this time. DPR printout notes an entry, 041:050270, which is a 5-line memo indicating that a negative, single-dose acute delayed neurotoxicity study was submitted to EPA. DPR has no current need for this study, nor for any other neurotoxicity study in support of this compound.